Dyspepsia, Irritable Bowel Syndrome, and Hematological Parameters in Recurrent Aphthous Stomatitis

Rekürren Aftöz Stomatitde Dispepsi ve İrritabl Barsak Sendromu Sıklığı ile Hematolojik Parametreler

Gastrointestinal Complaints

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Özet

Amaç: Bu çalışmanın amacı rekürren Aftöz Stomatit Hastalarında gastrointestinal sistem şikâyetleri (dispepsi, İrritabl Barsak Sendromu) ile hematolojik parametreler arasında ki ilişkiyi araştırmaktır. Gereç ve Yöntem: Çalışmaya ağız mukozasında tekrarlayan aft tanısı alan ve Behçet hastalığı tanısı olmayan 44 rekürren aftöz stomatit hastası dahil edildi. Hastalara oral aftın özelliklerini, dispepsi şikâyetlerini ve irritabl barsak sendromunun tanısında kullanılan Roma 3 kriterlerini içeren anket soruları soruldu. Hematolojik sonuçları retrospektif olarak değerlendirildi. Rutin hematoloji taraması ile hemoglobin, vitamin B12, folik asit ve TSH değerleri retrospektif olarak analiz edildi. Tüm veriler SPSS program ile değerlendirildi. Bulgular: Konstipasyon şikayeti kadınlarda erkeklerden daha sık görüldü(%59.3 karşı 11.8%, p<0.05). Hematolojik parametrelere bakıldığında, aftsız olarak geçirilen süre ile aftın boyutu (r= 0,343; p= 0,026) ve lenfosit düzeyi (r= 0,383; p=0,028) arasında pozitif yönlü orta düzeyde istatistiksel olarak anlamlı bir korelasyon mevcuttu. Buna karşın aftsız geçen süre ile yaş(r:0.112; p:0.473) ve aftın tekrarlama sıklığı(r:0.05; p:0.738) ve vitamin B12(r:0.19; p:0.929) ile Hb seviyeleri(r:0.047; p:0.781) arasında istatistiksel olarak anlamlı bir ilişki bulunmadı.

Anahtar Kelimeler

Rekürren Aftöz Stomatit; Lenfosit; Gastrointestinal Hastalıklar; Demir Eksikliği Anemisi; Folik Asit; Vitamin B 12

Abstract

Aim: The goal of this study was to investigate the relationship between gastrointestinal complaints (dyspepsia, irritable bowel syndrome) and hematological parameters among recurrent aphthous stomatitis (RAS) patients. Material and Method: Forty-four RAS patients with a diagnosis of recurrent oral ulcers in oral mucosa were included in this study. They answered a questionnaire concerning oral aphthous properties, dyspepsia problems, and irritable bowel syndrome. Routine hematological screening and hemoglobin, vitamin B12, folic acid, and TSH were analyzed retrospectively. Data analyses were performed using SPSS. Results: Constipation complaints by females were statistically more frequent than those of males (59.3% vs. 11.8%; p<0.05). There was a positive, statistically moderate and significant correlation between the time passed without having an aphtha (r=0.343; p=0.026) and lymphocyte level (r=0.383; p=0.028). However, there was no association between the time passed without having an aphtha and age (r=0.112; p=0.473), aphtha recurrence frequency (r=0.05; p=0.738), vitamin B12 (r=0.019; p=0.929), and Hb levels (r=0.047; p=0.781). Discussion: It was determined that there was positive correlation between aphtha size and lymphocyte level. Further studies should be designed in light of the association of RAS and gastrointestinal system disease.

Keywords

Recurrent Aphthous Stomatitis; Lymphocytes; Gastrointestinal Diseases

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Introduction

Recurrent aphthous stomatitis (RAS), characterized by painful and recurrent mucosal ulceration, is one of the most common causes of ulcerations in the mouth. The etiopathogenesis of the disease is not exactly known [1]. Recent studies have shown that several gene polymorphisms in TLR2, TLR4, NLRP3, and CD86 are associated with RAS [2-6]. In addition to genetic predisposition factors, emotional stress, trauma, atopy, drug reactions, nutritional deficiencies, hematological and immunological disorders, hormonal changes, and microbial agents, especially Helicobacter pylori, are responsible for the occurrence of the disease [7-8]. These are also factors in the etiology of dyspepsia and irritable bowel syndrome [9].

Recurrent aphthous ulcers have been reported to affect anywhere from 2% to 66% of the world population; however, its prevalence is not exactly known because of its episodic course [6]. Increased frequency of the disease has been reported due to parameters such as gender (female), age (<40 years), ethnic variation (white race) [10], and socioeconomic status (frequently in developed countries) [11-12].

The three main clinical types of RAS are minor, major, and herpetiform [13]. Minor aphtha (Miculiz's aphthae) is the most common type (90–95% of all cases). The aphthous ulcers may be single or multiple lesions with diameters less than 5 mm. These aphthous ulcers heal without scarring and last between one and two weeks.

Major aphtha is the rarer but more painful type of the disease. In this form, the aphthous ulcers are larger than 1 cm and heal in approximately six weeks with scarring. Herpetiform aphthae occur in the oral mucosa as lesion grubs of 2-3 mm diameter. They are irregular and superficial ulcerations. They heal in 10-14 days without scarring [11].

Because the etiopathogenesis of RAS is still unclear, socio-demographic characteristics, GIS complaints, and hematological findings of RAS patients are examined to contribute to a better understanding of the etiopathogenesis.

Material and Method

A total of 44 patients with a diagnosis of recurrent oral ulcerations in the oral mucosa were recruited from University Hospital Dermatology and Internal Affairs Polyclinics. The exclusion criteria were diagnosis of Behçet's disease and age below 18. All patients were requested to participate in a face-to-face interview to reply to a questionnaire that included questions about dyspeptic complaints and Roma 3 criteria, used in the diagnosis of irritable bowel syndrome. The questionnaire also included questions regarding: family history of aphtha, aphtha size, localization, and frequency, smoking status and alcohol consumption, continuous use of prescribed drugs, the occurrence of systemic diseases, aphtha/stress relationship, epigastric pain, epigastric burning, epigastric discomfort, epigastric heartburn, brackish water in the mouth, nausea, vomiting, belching, indigestion, early satiety, stomach bloating, stomach gas, abdominal pain, whether abdominal pain heals with defecation or not, whether the start of the pain occurs with changes in the frequency of bowel movements and/or changes in the shape or appearance of the stools, abdominal bloating, constipation, diarrhea, irregular bowel movements, and complaints of stool mucus. The hematological parameters were evaluated retrospectively.

Data were analyzed using SPSS 19.0 package software. The frequency, percentage, mean, standard deviation, median, minimum, and maximum values were used in describing the characteristics of the patients. The relationships between aphtha and GIS complaints were examined by chi-square test. The parameters such as age, time passing without aphtha, and frequency of aphtha recurrence were analyzed using Pearson's correlation analysis. Also, the relationship between the size of aphtha and hematological parameters were analyzed by Pearson's correlation. The obtained data revealed that hemoglobin (Hb) and vitamin B12 values had normal distribution. However, non-parametric tests were used because the number of participants was less than 30 in both groups. In the study group, the relationship between gender by age and hematological parameters was analyzed using the Mann-Whitney U-test.

Results

Of the patients, 61.4% percent were female (n=27) and 38.6% were male (n=17). The average age was 37.9±15.2 (min-max: 18-67) years. 65.9% of the patients expressed that they had no health problems and 61.4% reported that they were not taking any drugs. 38.6% of the patients reported that they use antihypertensive medications. 4.5% of the patients were smokers and 2.3% of the patients consumed alcohol. 63.6% of the patients expressed that they experienced stress. 55.8% of the patients reported that they experienced RAS a few times in a month, 25.6% always experienced RAS, and 18.6% experienced RAS three to four times a year.

53.5% of the patients stated they had no complaints of the GIS. 37.2% of the patients reported having GIS complaints for longer than one year, 7% had complaints for one year, and 2.3% had complaints for three months. 48.8% of the patients with GIS complaints had a family history of aphtha; 37.2% had epigastric pain; 38.6% had epigastric burning; 34.1% had epigastric discomfort; 38.6% had epigastric heartburn; 40.9% had brackish water in the mouth; 22.7% had nausea; 6.8% had vomiting; 36.4% had burping; 37.2% had indigestion; 22.7% had early satiety; 45.5% had stomach bloating; 43.2% had stomach gas; 25% had stomach aches; 34.1% had abdominal bloating; 40.9% had constipation; 4.5% had diarrhea; 25% had irregular bowel movements; and 6.8% had complaints of mucus in the stool. No statistically significant relationship was found among GIS complaints by gender, except for constipation ($p>0.05$). Constipation complaints by females were statistically more frequent than those by males (59.3% vs. 11.8%; $p<0.05$).

Hematological parameters according to gender are shown in Table 1. The average Hb value was 13.38±0.78 in females and 12.80±1.55 in males. The average serum ferritin value was 47.54±62.68 in females and 76.55±103.53 in males. The average vitamin B12 value was 455.23±213.88 in females and 398.33±175.65 in males.

When examining the aphthae size distribution in the current study, 25 patients (59.5%) had minor, 16 patients (38.1%) had major, and one patient (2.4%) had herpetiform aphthae.

The average hematological parameters according to aphthae size are shown in Table 2. There was no statistically significant

Table I. Variation of hematological parameters according to gender

Variables	Female (n=27)				Male (n=17)				p
	Mean	Standart deviation	Medium	Min-Max	Mean	Standart deviation	Medium	Min-Max	
Age	36,44	15,26	34,00	18,00-67,00	40,18	15,24	34,00	19,00-66,00	0,329
Hemoglobin	11,72	3,90	12,75	0,00-14,50	13,01	3,76	14,40	0,00-16,80	0,021*
Vitamin B12	402,35	251,58	306,50	187,00-1000,00	508,00	511,79	304,00	179,00-2000,00	0,443
Folat	7,18	2,30	6,69	4,06-15,50	10,33	4,95	8,64	4,26-18,30	0,073
Lymphocyte	1,91	0,53	1,90	0,70-3,10	1,94	0,70	1,80	0,80-3,10	0,767
MPV	8,72	0,96	8,70	7,00-11,10	9,17	1,35	8,90	7,20-12,10	0,376

*p<0,05 Mann-Whitney U test

Table II. The relation of hematological variables and aphtha size

Hematological variables	Aphtha Size	N	Mean ± SD
Hemoglobin	Minor	20	13.50±1.30
	Major	12	13.18±1.40
Platelets	Minor	19	242631.6±64783.58
	Major	12	248416.7±69353.45
MPV	Minor	20	9.14±1.31
	Major	12	8.81±0.77
Neutrophils/Lymphocyte ratio	Minor	20	4.04±0.99
	Major	11	4.39±1.13
Lymphocyte	Minor	20	1.85±0.50
	Major	11	1.99±0.73
Vitamin B12	Minor	12	398.91±164.74
	Major	10	393.40±272.12
Folat	Minor	12	8.70±4.34
	Major	11	8.46±4.40
TSH	Minor	12	1.84±0.87
	Major	7	3.94±4.83

SD: Standard deviation

difference between aphthae sizes according to average hematological parameters (p>0.05).

There was a positive, statistically moderate and significant correlation between the time passed without having an aphtha (r=0.343; p=0.026) and lymphocyte level (r=0.383; p=0.028). A statistically significant correlation was not found among the time passed without having an aphtha and age (r=0.112; p=0.473), aphtha recurrence frequency (r=0.05; p=0.738), vitamin B12 (r=0.019; p=0.929), and Hb levels (r=0.047; p=0.781). There was no statistically significant correlation among age, aphthae recurrence frequency, vitamin B12, and folate levels (r= -0.259 p= 0.093; r= 0.290 p= 0.159; r=0.27 p= 0.177, respectively). There was no statistically significant correlation among aphthae recurrence frequency, vitamin B12 levels, and the time passed without having an aphtha (r=0.31 p= 0.146; r= 0.05 p= 0.738, respectively). There was no correlation among the aphtha size, age, and aphtha recurrence frequency (r= 0.017 p=0.915; r= 0.167 p= 0.292). There was no correlation between the aphtha size, Hb, and vitamin B12 (r=-0.153 p=0.373; r=-0.087 p=0.694).

Discussion

Because the pathogenesis of RAS is not fully understood, no curative treatment has been achieved yet. The presence of RAS on oral mucosa reduces quality of life because of its chronic and recurrent course [14]. In addition, there are no effective treatments or curative therapeutic agents for the aphthous stomatitis.

The literature states that RAS is seen more frequently in females than in males; the result of the current study is in line with the literature [15].

In recent years, some systemic drugs have been found to trigger oral ulcerations similar to RAS in some isolated cases. However, these ulcers are not recurrent, and so are resolved when the drugs are discontinued [16]. In a study by Atılganoğlu et al. [17], a relationship was found between analgesics and antibiotics and aphthae. Other drugs associated with RAS include: β-blockers, captopril, gold salt, Nicorandil, phenobarbital, sodium hypochlorite, anticoagulants, acetylsalicylic acid, D-penicillamine, gold, sodium thiomalate, immunosuppressants, and interferon [18]. The current study revealed that most of the patients (61.4%) did not take any prescribed drugs. Patients who were taking drugs (38.6%) mostly used antihypertensive drugs. In our study there was no relationship between RAS and drugs because our patients had RAS lesions before taking drugs.

The protective effect of smoking on RAS development has been reported. The underlying reason is keratinization of the oral mucosa and the anti-inflammatory effects of nicotine [18-19]. In a study conducted in Turkey, it was determined that only 8.8% of RAS patients were smokers [19]. Similarly, in our study, the relationship between smoking and RAS was quite low (4.5%). The relationship between RAS and alcohol use has been less frequently investigated compared to the relationship between smoking and RAS. Pentenero et al. [20], in a study of 4098 patients with oral mucosal lesions, found no statistically significant relationship between RAS and alcohol; similarly, in our study alcohol use was only 2.3%. In the literature there are conflicting results about the relationship between stress and RAS [14, 20-21]. It is stated that individuals with certain personality traits are more prone to develop RAS [14]. The exact mechanism of stress as an aphthous stimulant is not yet understood [11]. In our study there is a relationship between the occurrences of aphthous lesions and stress similar to that found in the literature.

Oral ulcerations that are similar to RAS are seen in Behcet's disease, MAGIC syndrome, gluten-sensitive enteropathy (celiac disease), inflammatory bowel diseases (Crohn's disease and ulcerative colitis), and systemic diseases such as cyclic neutropenia, as well as benign or malignant tumors [1, 7, 13]. The term 'RAS' is used for ulcerations that are formed in the absence of underlying systemic disease, are located in the oral mucosa, and are painful and recurrent. [7]. In the current study, there

were no complaints of GIS in a majority of the patients (53.5%); almost half of the patients (48.8%) who had GIS complaints had aphthae in their family history. Frequently seen GIS complaints included bloating in the stomach (45.5%), stomach gas (43.2%), GIS reflux (40.9%), and constipation symptoms (40.9%). There was no statistically significant relationship between GIS complaints and gender, except for constipation ($p > 0.05$). Women complained of constipation at a statistically significant higher level compared to males (59.3% vs. 11.8%; $p<0.05$).

Previous studies have reported that nutritional deficiencies play a role in the etiology of RAS [1, 13, 22]. The role of iron, folic acid, and vitamin B12 deficiency in the pathophysiology of RAS is not entirely known. There are studies in the literature on this subject that contradict each other [8,13, 22-24]. In a study by Porter et al. [23] in which they examined the ferritin, vitamin B12, and folic acid levels of RAS patients, only low levels in ferritin were statistically significant. Aras et al. [24] identified 11% (7 patients) of their patients as lacking vitamin B12, but after vitamin B12 supplementation, very few of these patients (2 patients) improved, while others continued to relapse. In addition, vitamin deficiencies can adversely affect the immune system, which could partly explain the association with RAS [10]. Khademi et al. [8] have demonstrated that antioxidant vitamins (A, E, and C) are not associated with RAS. Therefore, even though additional supplementation of vitamins is effective during initial treatment, the continuation of relapses of RAS supports the assumption that nutritional deficiency is not the only factor in aphthae development.

Autoimmune disease affects the gastrointestinal system (GIS) more than the others. Important evidence has recently been reported that RAS is autoimmune in origin. We have evaluated GIS related parameters to examine the association between RAS and GIS. Thus, recurrent aphthous stomatitis may have direct effects on the GIS because its underlying cause is related to autoimmunity. In studies examining the role of lymphocytes on RAS formation, lymphocyte dysfunction and severe cytotoxicity in lymphocytes were observed, and either circulating humoral antibodies or sensitized T lymphocytes acting against the oral mucosal epithelium are shown in aphthous ulcer patients [25]. In the current study we have found a positive correlation between aphtha size and lymphocyte level, similar to previous studies. Thus, a patient's complaints of long-duration and major aphthous ulcerations, along with a high lymphocyte level, should be referred to the internal medicine department to check for GIS disorders. Still the stimulating mechanism of the sensitized lymphocytes that is formed before ulceration is not yet known, the autoinflammation and autoimmunity is important to lighten up the both disease.

Conclusions

GIS organs are the most affected by autoimmune diseases. The oral mucosa is a part of the GIS, and thus RAS is common in autoimmune diseases. According to the data we obtained, there is a complex relationship between RAS and autoimmunity and lymphocyte dysfunction. RAS is also a multifactorial disease that can be related to GIS complaints. These factors should be taken into account in explaining the etiopathogenesis of RAS and in the evaluation, monitoring, and treatment of patients.

Competing interests

The authors declare that they have no competing interests.

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